Freshly Thawed Cryobanked Human Neural Stem Cells Engraft within Endogenous Neurogenic Niches and Restore Cognitive Function after Chronic Traumatic Brain Injury.

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Authors: Anna Badner, Emily K Reinhardt, Theodore V Nguyen, Nicole Midani, Andrew T Marshall, Cherie A Lepe, Karla Echeverria, Javier J Lepe, Vincent Torrecampo, Sara H Bertan, Serinee H Tran, Aileen J Anderson, Brian J Cummings

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Public Summary:
Human neural stem cells (hNSCs) have potential as a cell therapy after traumatic brain injury (TBI). While various studies have demonstrated the efficacy of human neural stem cells that are generated during continuous cell culture, there is a significant gap in our understanding of freshly thawed cells from cryobanked (frozen) stocks of human neural stem cells, which would be a more clinically relevant cell source. To address these shortfalls, the therapeutic potential of our previously validated Shef-6.0 human embryonic stem cell (hESC)-derived hNSC line was tested after long-term cryostorage and thawing before transplant into TBI animals. Immunodeficient athymic nude rats received a moderate TBI and four weeks, 600,000 freshly thawed hNSCs were transplanted into the brain. Three months later, we found that >50% of cells survived the transplant. Most hNSCs were engrafted in the meninges, a layer the covers and protects the brain, and the lining of the lateral ventricles. The majority of the hNSCs remained as undifferentiated progenitors. Importantly, transplantation resulted in improved spatial learning and memory in Morris water maze navigation and reduced risk taking in an elevated plus maze. Investigating potential mechanisms of action, we identified an increase in host hippocampal neurons, improvements in the morphology of host cells, and a long term reduction in inflammation. Together, these findings validate the potential of hNSCs to improve function after TBI and demonstrate that long-term biobanking of cells and thawing aliquots before use may be suitable for clinical deployment

Scientific Abstract:
Human neural stem cells (hNSCs) have potential as a cell therapy after traumatic brain injury (TBI). While various studies have demonstrated the efficacy of NSCs from ongoing culture, there is a significant gap in our understanding of freshly thawed cells from cryobanked stocks-a more clinically relevant source. To address these shortfalls, the therapeutic potential of our previously validated Shef-6.0 human embryonic stem cell (hESC)-derived hNSC line was tested after long-term cryostorage and thawing before transplant. Immunodeficient athymic nude rats received a moderate unilateral controlled cortical impact (CCI) injury. At four weeks post-injury, 6 x 10(5) freshly thawed hNSCs were transplanted into six injection sites (two ipsi- and four contra-lateral) with 53.4% of cells surviving three months post-transplant. Interestingly, most hNSCs were engrafted in the meninges and the lining of lateral ventricles, associated with high CXCR4 expression and a chemotactic response to SDF1alpha (CXCL12). While some expressed markers of neuron, astrocyte, and oligodendrocyte lineages, the majority remained progenitors, identified through doublecortin expression (78.1%). Importantly, transplantation resulted in improved spatial learning and memory in Morris water maze navigation and reduced risk taking in an elevated plus maze. Investigating potential mechanisms of action, we identified an increase in ipsilateral host hippocampus cornu ammonis (CA) neuron survival, contralateral dentate gyrus (DG) volume, and DG neural progenitor morphology as well as a reduction in neuroinflammation. Together, these findings validate the potential of hNSCs to improve function after TBI and demonstrate that long-term biobanking of cells and thawing aliquots before use may be suitable for clinical deployment.

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